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95. The method of Claim 44 wherein the combination is administered in a substantially simultaneous manner.

**METHOD OF USING A CYCLOOXYGENASE-2 INHIBITOR AND ONE OR
MORE ANTINEOPLASTIC AGENTS AS A COMBINATION THERAPY IN
THE TREATMENT OF NEOPLASIA**

5 **Field of the Invention**

The present invention relates to combinations and methods for treatment or prevention of neoplasia disorders in a mammal using two or more components with
10 at least one component being a cyclooxygenase-2 inhibitor.

Background of the Invention

A neoplasm, or tumor, is an abnormal, unregulated,
15 and disorganized proliferation of cell growth. A neoplasm is malignant, or cancerous, if it has properties of destructive growth, invasiveness and metastasis. Invasiveness refers to the local spread of a neoplasm by infiltration or destruction of surrounding
20 tissue, typically breaking through the basal laminas that define the boundaries of the tissues, thereby often entering the body's circulatory system. Metastasis typically refers to the dissemination of tumor cells by lymphatics or blood vessels. Metastasis also refers to
25 the migration of tumor cells by direct extension through serous cavities, or subarachnoid or other spaces. Through the process of metastasis, tumor cell migration to other areas of the body establishes neoplasms in areas away from the site of initial appearance.

30 Cancer is now the second leading cause of death in the United States and over 8,000,000 persons in the United States have been diagnosed with cancer. In 1995,

cancer accounted for 23.3% of all deaths in the United States. (See U.S. Dept. of Health and Human Services, National Center for Health Statistics, Health United States 1996-97 and Injury Chartbook 117 (1997)).

- 5 Cancer is not fully understood on the molecular level. It is known that exposure of a cell to a carcinogen such as certain viruses, certain chemicals, or radiation, leads to DNA alteration that inactivates a "suppressive" gene or activates an "oncogene".
- 10 Suppressive genes are growth regulatory genes, which upon mutation, can no longer control cell growth. Oncogenes are initially normal genes (called proto-oncogenes) that by mutation or altered context of expression become transforming genes. The products of
- 15 transforming genes cause inappropriate cell growth. More than twenty different normal cellular genes can become oncogenes by genetic alteration. Transformed cells differ from normal cells in many ways, including cell morphology, cell-to-cell interactions, membrane content,
- 20 cytoskeletal structure, protein secretion, gene expression and mortality (transformed cells can grow indefinitely).

- Cancer is now primarily treated with one or a combination of three types of therapies: surgery,
- 25 radiation, and chemotherapy. Surgery involves the bulk removal of diseased tissue. While surgery is sometimes effective in removing tumors located at certain sites, for example, in the breast, colon, and skin, it cannot be used in the treatment of tumors located in other
- 30 areas, such as the backbone, nor in the treatment of disseminated neoplastic conditions such as leukemia.